



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/14, 9/22	A1	(11) International Publication Number: WO 85/ 03436 (43) International Publication Date: 15 August 1985 (15.08.85)
(21) International Application Number: PCT/DK85/00005 (22) International Filing Date: 8 February 1985 (08.02.85) (31) Priority Application Numbers: 620/84 621/84 (32) Priority Dates: 10 February 1984 (10.02.84) 10 February 1984 (10.02.84) (33) Priority Country: DK (71) Applicant (for all designated States except US): A/S ALFRED BENZON [DK/DK]; Halmtorvet 29, DK-1700 Copenhagen V (DK). (72) Inventors; and (75) Inventors/Applicants (for US only) : KJØRNÆS, Kim [DK/DK]; Trekronergade 25, DK-2500 Valby (DK). CHRISTENSEN, Finn, Norring [DK/DK]; Stumpe-dyssevej 13, DK-2970 Hørsholm (DK). JENSEN, Jens, Rasmus [DK/DK]; Rosendalsvej 12, DK-3660 Stenløse (DK).		(74) Agent: PLOUGMANN & VINGTOFT; Staunings Plads 3, DK-1607 Copenhagen V (DK). (81) Designated States: AU, BR, DK, FI, JP, KR, NO, US. Published <i>With international search report.</i>

(54) Title: DIFFUSION COATED MULTIPLE-UNITS DOSAGE FORM

(57) Abstract

In an oral pharmaceutical controlled release multiple-units formulation, individual units containing an active substance are coated with a substantially water-insoluble, but water-diffusible controlled release coating which includes 1) an inner film layer which causes adhesion between the units at elevated temperatures, comprising a water-dispersible film-forming agent, and 2) an outer film layer comprising a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units. The inner film layer may additionally comprise a substance which is capable of forming a continuous phase. By subjecting the thus coated units to heating to accelerate the formation of a continuous phase of the film-forming agent of the inner layer and optionally also of the additional substance, a coating is formed which substantially does not change its diffusion characteristics in the course of time.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
BB	Barbados	HU	Hungary	NL	Netherlands
BE	Belgium	IT	Italy	NO	Norway
BG	Bulgaria	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali		
FR	France				

DIFFUSION COATED MULTIPLE-UNITS DOSAGE FORM

The present invention relates to an oral pharmaceutical controlled release multiple-units dosage form in which individual units containing an active substance are coated with a water-based diffusion coating.

5 TECHNICAL BACKGROUND

Many physiological factors influence both the gastrointestinal transit time and the release of a drug from a controlled release dosage form and thus the uptake of the drug into the systemic circulation. Dosage forms should therefore be designed so that such variable factors do
10 not compromise the efficacy and safety of the product.

In humans, a reproducible gastrointestinal transit time of a depot formulation can be achieved only by a controlled release multiple-units dosage form.

The term "controlled release multiple-units formulation" (Bechgaard &
15 Hegermann Nielsen, 1978) indicates a pharmaceutical formulation comprising a multiplicity (typically at least 100) of individual coated (or "microencapsulated") units contained in the formulation in such a form that the individual units will be made available from the formulation upon disintegration of the formulation in the stomach of animals,
20 including humans, who have ingested the formulation. Typically, the multiple-units formulation may be a capsule which disintegrates in the stomach to make available a multiplicity of individual coated units contained in the capsule, or a tablet which disintegrates in the stomach to make available a multiplicity of coated units originally combined in
25 the tablet.

Drug release from a controlled release dosage form is generally controlled either by *diffusion* through a coating or by *erosion* of a coating by a process dependent on, e.g., enzymes or pH. The importance of a pH independent diffusion with respect to obtaining a reproducible
30 rate of availability and to minimizing intra- and intersubject variations

is known (GB Patent No. 1 468 172 and Bechgaard & Bagg sen, 1980). It is also known that controlled drug release *in vivo* can be achieved through an erodible process by enteric coating of a multiple-units dosage form (Green, 1966; McDonald *et al.*, 1977; Bogen-
5 toft *et al.*, 1978).

Both above-mentioned types of controlled release multiple-units formulation techniques aim at a controlled release of active substance in a predetermined pattern to reduce and delay the peak plasma concentration without affecting the extent of drug availability. Due to a
10 lower peak plasma concentration, the frequency of undesirable side-effects may be reduced, and due to the delay in the time it takes to obtain the peak plasma concentration and the prolongation of the time at the therapeutically active plasma concentration, the dosage frequency may be reduced to a dosage taken only twice or once a day,
15 in order to improve patient compliance.

A further advantage of the controlled release multiple-units dosage form is that high local concentrations of the active substance in the gastrointestinal system is avoided, due to the units being distributed freely throughout the gastrointestinal tract, independent of gastric
20 emptying. If the mucosa of the stomach is more sensitive to the active substance than the intestinal mucosa, controlled release formulations avoiding release of active substance in the gastric area will be preferred; formulations of this type are controlled release multiple-units formulations in which the coatings are substantially resistant to gastric
25 conditions.

The present invention deals with multiple-units dosage forms which are diffusion coated.

In the known art preparation of diffusion coated controlled release multiple-units formulations, diffusion film-coating mixtures have been
30 used which contain synthetic film-forming agents dissolved or dispersed in organic solvents, e.g. isopropanol, ethanol, acetone, or mixtures thereof. However, although these mixtures show advantages in that the film-forming agents are diffusion controlling *per se*, that

is, without any modification or addition, and the film formed is n n-tacky, th y suffer from s ri us disadvantages from an environm ntal and process-econ mic point of view:

- 5 The use of organic solvents gives rise to environmental pollution, danger of explosion, and health hazards unless costly recycling procedures are used, such as recycling in scrubber towers, and the fact that the film coating mixtures have a low dry matter content (normally less than 15% by weight), incurs long processing periods resulting in a low process efficiency.
- 10 From an environmental and process-economic point of view, water-based film-coating mixtures are more desirable; the present invention concerns developments relating to water-based film coatings.

DISCLOSURE OF THE INVENTION

- 15 A number of coatings employed in connection with pharmaceutical controlled release multiple-units formulations and based on water-dispersible film-forming agents have been observed to suffer from th disadvantage that they change their release characteristics in th course of time due to the fact that a coagulation and consequently formation of a continuous phase proper of the film-forming agent only
- 20 occurs over a longer period of time. This means that it is not possible to maintain a reproducible release rate of an active substance contained in the multiple-units formulation as a decreasing release rate has been observed for such coatings. In accordance with the present invention, it has surprisingly been found that by heating
- 25 units coated with such coatings, the formation of a continuous phas of the film-forming agent and the relaxation of the long, intertangled polymer chains of the film-forming agent, that is, the chains are relaxed to their lowest possible energy level, is accelerated so that the r sulting coating will be a diffusion coating which substantially
- 30 do s not chang its diffusion charact ristics in th course f tim , whereby storag stability is imparted to th pharmaceutical comp si-tion comprising th coated units.

Thus, an aspect of the present invention relates to a method of preparing an oral pharmaceutical controlled release multiple-units formulation in which

- 5 a) individual units containing an active substance are coated with a coating composition comprising an aqueous dispersion of a film-forming agent to form an inner film layer which causes adhesion between the units at elevated temperatures,
- 10 b) the thus coated units are provided with an outer film layer of a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the coated units, and
- 15 c) the coated units are subsequently heated to a temperature at which the inner film layer is tacky, and at which the formation of a continuous phase of the film-forming agent is accelerated, and subsequently cooled, whereby a coating which substantially does not change its diffusion characteristics in the course of time is formed.

The inner film layer may additionally comprise a substance which is capable of forming a continuous phase, the presence of which substance imparts specific desirable characteristics to the final coating, especially with respect to the formation of a coating which delays and controls the diffusion through the inner film layer in a useful and reproducible manner to confer desirable controlled release characteristics to the coated units. When used in connection with this additional substance, the term "capable of forming a continuous phase" is intended to indicate that the substance is capable, in itself, that is, without admixture with other components, of forming a continuous phase (that is, either by being molten or by being dissolved and subjected to removal of the solvent), and that it forms a homogeneous lattice-like structure in the inner layer. The term "homogeneous" is intended to indicate that, throughout the inner layer, the two components are present in the same proportions and uniformly distributed in each other. In the present context, the term "diffusion coating"

indicates a coating which does not disintegrate or dissolve in water, but which gradually lets the active substance in the units pass through. The term is intended to include the so-called enteric coatings which at an acid pH have properties similar to those of the conventional diffusion coatings.

When an additional substance is incorporated in the inner layer, the coated units are also subjected to elevated temperatures, either to cause formation of a continuous phase of the substance in question in the film-forming agent concurrently with accelerating the formation of a continuous phase of the film-forming agent as described above or solely to accelerate the formation of a continuous phase of the film-forming agent, which may be further impeded by the presence of the substance which may constitute a steric hindrance to the coagulation of the film-forming agent to further prolong the period needed for the film-forming agent to form a continuous phase.

An example of a substance which needs heating to form a continuous phase in the inner film layer is a hydrophobic substance which contributes to delaying and controlling diffusion through the inner layer. It has in fact surprisingly been found that by incorporating a hydrophobic substance in the inner layer, it may be possible to use film-forming substances which are not in themselves diffusion-controlling as diffusion-controlling coatings, and water-dispersible film-forming substances which in themselves are diffusion-controlling are improved to obtain a more efficient diffusion control, both combining the inherent advantages of the diffusion controlled release multiple-units formulations and the easy, economic, and hazard-free application of water-based coating mixtures. In order to contribute to the sustained release effect, however, the hydrophobic substance should be present in the form of a film which is homogeneously mixed with the film of the film-forming substance. Therefore, the units coated according to steps a) and b) in the method outlined above, after which the hydrophobic substance is present in the inner film layer as a dispersed phase, are suitably heated to a temperature above the melting point of the hydrophobic substance which, on melting and subsequent cooling, forms a continuous phase in the inner film layer in homoge-

neous admixture with the film-forming agent. The hydrophobic substance is preferably present in the coating composition in the form of a suspension of particles thereof.

5 An example of a substance which delays the coagulation of the film-forming agent in the inner film layer is a polymeric substance which prevents adhesion between the units during coating and which, in the final coating, is homogeneously admixed with the continuous phase of the film-forming agent in the inner layer imparting compressibility to the coating. In the present context, the term "compressibility" when
10 used to describe a property of the coating refers to a coating possessing a sufficient plastic deformability to result in no significant changes in the release characteristics of compressed coated units relative to non-compressed coated units. It has surprisingly been found that such compressibility may be provided by homogeneously
15 mixing the film-forming agent with a polymeric substance which functions as a reinforcing agent by imparting greater hardness as well as plastic deformability to the layer. When units coated according to steps a) and b) above are heated, coagulation of the film-forming agent is accelerated, and the film-forming agent forms a continuous
20 phase in homogeneous admixture with the polymeric substance so that a reproducible release rate of the active substance in the units is obtained.

The water-dispersible film-forming agents contemplated for the purpose of the present invention are pharmaceutically acceptable film-
25 forming polymers which are substantially water-insoluble, but which permit water diffusion. Examples of such substances are cellulose derivatives, silicone polymers and copolymers, vinyl polymers and copolymers, acrylic polymers and copolymers and biodegradable polymers such as polyamino acids, polylactic acid and copolymers and
30 derivatives thereof, or mixtures thereof. More specifically, the film-forming substance is selected from ethylcellulose and a copolymerisation of anionic or non-ionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, celluloseacetatephthalate, polyvinylacetatephthalate and vinylacetate-crotonic acid copolymerisates.

When a hydrophobic substance is incorporated in the inner film layer according to the invention, it may be any pharmaceutically acceptable hydrophobic substance which will result in the desired retardation of the diffusion (in the present context, the term "hydrophobic" indicates substances which, relative to water, have a contact angle of more than 90°). All such hydrophobic substances are substances which in themselves are capable of forming a continuous phase. The amount of the hydrophobic substance incorporated will depend on the properties of the hydrophobic substance, in particular its hydrophobicity, with respect to retarding the water diffusion of the polymeric film.

Typical examples of such hydrophobic substances are substances selected from hydrocarbons and hydrocarbon derivatives, waxes, oils and fats, and mixtures thereof.

One class of hydrophobic substances which are interesting for the purposes of the present invention are waxy substances, examples of which are

natural waxes such as paraffin wax, microcrystalline wax, other mineral waxes, e.g. montan wax or ceresin wax; vegetable waxes, e.g. candelilla wax, carnauba wax or cocoa butter, or animal waxes, e.g. beeswax, spermaceti or wool wax,

synthetic waxes such as fatty alcohols and acids, e.g. cetyl alcohol, stearyl alcohol, stearic acid, palmitic acid or myristic acid, fatty esters and glycerides, e.g. glyceryl stearates, hydrogenated oils, e.g. hydrogenated castor oil, higher ketones, amines or amides, e.g. stearone or laurone, synthetic hydrocarbon waxes, synthetic animal waxes and other synthetic waxes,

and mixtures thereof.

The hydrophobic substances will often have a melting temperature below 200°C, more often below 150°C and usually below 100°C.

The hydrophobic substance, .g. a waxy substance such as paraffin wax, will normally be present in the inner film layer in an amount of between about 0.1 and 50%, in particular between 1 and 40%, especially between about 10 and 30%, by weight of the inner film layer.

- 5 When a polymeric substance is incorporated in the inner film layer according to the invention, it may be any pharmaceutically acceptable polymeric substance which will bring about the desired compressibility of the coating. As is the case with the hydrophobic substances, the polymeric substances to be employed according to the invention are
- 10 substances which, in themselves, are capable of forming a continuous phase. The amount of the polymeric substance incorporated will depend on the properties of the polymeric substance, in particular its film-forming properties and its hardness and plasticity. Apart from this, it is important that the polymeric substance is one which con-
- 15 tributes to imparting anti-adhesive properties to the inner film layer during coating.

- The polymeric substance is preferably a water-soluble polymeric substance as substances which are precipitated from an aqueous solution during the coating process are more easily homogeneously
- 20 admixed with the film-forming agent in the inner film layer. Typical examples of such polymeric substances are polyvinylpyrrolidone, polyalkylene glycols such as polyethylene glycol, and cellulose derivatives such as hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose,
- 25 carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

- The polymeric substance will normally be present in the inner film layer in an amount of between about 1 and 10%, in particular between
- 30 about 2 and 8%, especially about 4%, by weight relative to the amount of film-forming agent in the inner film layer. If the substance is a water-soluble substance, such as one of those mentioned above, it is important not to incorporate it in amounts which would significantly reduce or even destroy the sustained release effect.

It may be advantageous to incorporate an anti-adhesive in the inner film layer in order to avoid agglomeration of the units during the coating step as above. However, when the inner layer comprises a polymeric substance with an inherently anti-adhesive effect, it may only be necessary to add small amounts of this anti-adhesive (if any), which is desirable as the anti-adhesives usually employed for the present purpose do not contribute to the desired sustained release and often necessitate the use of larger amounts of coating material which, in turn, prolongs the coating process. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive, e.g. talc, is preferably incorporated in the coating in an amount of between about 0.1 and 50%, preferably between 1 and 40%, especially about 10-30%, such as about 15%, by weight of the inner film layer. The particle size of the anti-adhesive should normally be below about 40 μm , as by selecting a small particle size a larger surface area is obtained; the consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of anti-adhesive. The particle size should also be adapted so as to prevent sedimentation of the anti-adhesive in the coating mixture or blocking of jets and tubes in the coating equipment.

In most cases, it has been found that, when subjected to the elevated temperatures necessary to obtain the effect described above, the inner film layer tends to become tacky (adhesive) causing an undesirable agglomeration of the units. The tackiness on heating may either be due to an inherent property of the film-forming agent and is, in fact, a common characteristic of many water-dispersible film-forming agents, or it may be due to the presence of the additional substance described above.

- This latter, for instance, is the case with film layers containing a hydrophobic substance, as the formation of the continuous phase of the hydrophobic substance in homogeneous admixture with the film-forming substance necessary to provide the aimed-at additional sustained release is most conveniently performed by heating the units to a temperature above the melting point of the hydrophobic substance. This treatment, however, is not possible with coatings of this composition as the hydrophobic substance tends to become sticky or tacky with heating causing the units to agglomerate.
- 10 In both instances, i.e. both when the substance incorporated in the coating and when the film-forming agent itself causes adhesion, it is therefore necessary to provide the units with an additional, protective layer which is composed of a substance or a mixture of substances which is anti-adhesive at elevated temperatures and, preferably, also
- 15 imparts flowability to the coated units. In cases where a hydrophobic substance is incorporated in the inner layer, the outer layer should furthermore be one which, at temperatures above the melting point of the hydrophobic substance, is impermeable to the molten hydrophobic substance.
- 20 As a general rule, the film-forming agent in the outer film layer is one which is anti-adhesive at temperatures above about 40°C, especially temperatures above about 50°C, such as a temperature between about 60°C and about 120°C. The choice of a specific film-forming agent of the outer film layer may depend on the melting temperature
- 25 of a particular hydrophobic substance employed. However, additional criteria may also be applied to select a film-forming agent with the desired properties. For instance, it may in some cases be advantageous to provide a further sustained release effect, so the outer layer may also function as an additional diffusion barrier throughout the
- 30 gastrointestinal tract or be one which is dissolved in intestinal fluids only (an enteric coating). Furthermore, the outer layer may additionally contain an active substance which may either be the same substance as the one contained in the units, and which may for instance be designed for instant release, or which may be another drug advantageously administered simultaneously therewith. These additional
- 35

characteristics are not vital, however, and suitable film-forming agents for this purpose are found within most categories of film-forming agents. The film-forming agent of the outer layer is most preferably water-based, which means that the film-forming material is one which is either water-dispersible or water-soluble.

Examples of such agents are diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, celluloseacetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose and hydroxypropylmethylcellulose. The currently favoured film-forming agent for the outer layer is in fact hydroxypropylmethylcellulose although, as indicated above, it is water-soluble and thus does not contribute to delaying release. The layer of the protective film-forming agent need not be particularly thick, and is usually applied in an amount of about 0.1-10%, especially about 0.5-5%, in particular about 1% by weight of the uncoated units.

According to the invention, it has been found that the properties of the outer layer with respect to imparting improved flowability to the powder of the coated units may be considerably improved if a lubricant is incorporated therein in admixture with the film-forming agent. The lubricant is preferably present in the form of a finely divided, pharmaceutically acceptable powder, such as a metallic stearate, e.g. magnesium stearate or calcium stearate, microcrystalline cellulose, or a mineral substance such as titanium dioxide, calcite, calcium phosphate, calcium sulphate, colloidal silica, barium sulphate, hydrogenated aluminium silicates, or hydrous aluminium potassium silicates. Most preferably, the lubricant is talc.

Th individual units f th multiple-units formulati ns according to the inventi n will normally b ith r coated crystals or pell ts (coated cores). In the pellets, the core is constituted by a combination of active substance and excipients. A type of core which is widely used
5 in the known art (*vide*, e.g., European Patent Application, Publication No. 0 013 262) is a substantially spherical particle of a size of about 0.5 - 1 mm consisting of excipient(s) with active substance applied to its surface. Typical cores of this type are the so-called "non-pareil" cores where the excipients are in the form of spherical
10 particles of saccharose. It is also known, e.g., from GB Patent Specification No. 1 468 172, to prepare cores which are cross-sectionally substantially homogeneous. In the present context, the term "cores which are cross-sectionally substantially homogeneous" designates cores in which the active substance is not confined to an exterior
15 layer on the core body, in other words normally cores which, through the cross-section of the core body, contain substantially the sam type of composition comprising microparticles containing active substance, in contrast to the non-pareil type of cores which each consist of an excipient body with active substance applied to its surface, and
20 in contrast to coated crystal units which are substantially monolithic crystals. From this definition, it will be understood that the cores which are cross-sectionally substantially homogeneous will normally consist of a mixture of active substance with excipient(s), (and in spite of the term "homogeneous", this mixture will not necessarily b
25 qualitatively or quantitatively homogeneous through the cross-section of the particle but may show, e.g., a concentration gradient of one or more of its constituents) or they may consist substantially solely of active substance in a non-monolithic form, e.g. as a sintered mass of crystalline or amorphous particles of active substance. In the follow-
30 ing specification and claims, such cores which are cross-sectionally substantially homogeneous will, for the sake of brevity, often simply be designated "c r s".

Th oral pharmaceutical contr lled release multipl -units f rmulati n according to the inv nti n will typically be a capsule containing a
35 multiplicity of th units, typically more than 100, a sachet containing a multiplicity f th units, typically more than 1000, or a tablet made

from a multiplicity of the units, typically more than 100, in such a manner that the tablet will disintegrate substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout the gastro-intestinal tract.

- 5 The pharmaceutical formulation of the invention may also be one in which units of the type described above, that is, diffusion coated units are combined with uncoated units which comprise the same or another active substance for instant release thereof, and/or with non-diffusion coated units which have been provided with a coating
10 selected from hydrophilic coatings, hydrophobic coatings, water-based coatings and organic coatings imparting desired properties to the unit such as acid or alkali resistance, storage stability, taste masking, light stability, colouring, improved processability, etc. The ratio between diffusion coated and uncoated or non-diffusion coated units
15 in the composition may be adjusted according to, for instance, the desired release characteristics of the composition, but is preferably in the range of about 10:90 - 90:10 of diffusion coated units to uncoated or non-diffusion coated units.

- The formulations mentioned above may be prepared by conventional
20 methods known in the pharmaceutical industry. One particularly interesting shape of a tablet according to the invention, in particular when the tablet is to contain a rather large amount of active substance and is to be easy to swallow, is a shape substantially corresponding to a cylinder with rounded ends, a raised area circumscribing the periphery of the cylinder in the form of a flat belt and a
25 score dividing the cylinder, but not the peripheral belt, into two parts, substantially as shown in the drawing. As an example of such tablets may be mentioned tablets in which the active substance is potassium chloride crystals, e.g. in tablet sizes comprising 600 mg and 750 mg of potassium chloride, respectively, for use as potassium
30 supplement for patients in diuretic treatment.

In another aspect, the present invention relates to an oral pharmaceutical controlled release multiple-units formulation with the characteristics specified above which may be summarized as follows: indivi-

dual units containing an active substance which are coated with a substantially water-insoluble, but water-diffusible controlled release coating which includes

- 1) an inner film layer which causes adhesion between the units at elevated temperatures, comprising a water-dispersible film-forming agent, and
- 2) an outer film layer comprising a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units.

10 DETAILED DESCRIPTION OF THE INVENTION

Crystals

When the units coated according to the invention are crystals, they normally have a size between about 0.1 and 1.5 mm, preferably between about 0.4 and 1.0 mm. As an important example of an active substance which is suitably used in the form of crystals, potassium chloride may be mentioned.

Cores

According to the invention, the cores are preferably cross-sectionally substantially homogeneous cores.

- 20 The cores are typically made by granulating particles of the active substance together with excipients, including bulk agents such as carbohydrates and derivatives thereof such as starch and starch derivatives, including microcrystalline cellulose, binders such as cellulose derivatives, including methylcellulose or hydroxypropylmethylcellulose, polyethylene glycol, polyvinylpyrrolidone, agar, or gelatin, for instance by treatment in a high speed mixer (to directly obtain compact-shaped cores), or by treatment in a planetary mixer with subsequent extrusion of the mixture into strings of a predetermined

diameter approaching the desired final cross-sectional dimension of the cores and treatment of the strings in a marumerizer or similar equipment to obtain compact-shaped cores. The diameter of the cores is normally adapted so that the diameter of the coated core is about 5 0.1-1.5 mm, in particular about 0.4-1.0 mm, e.g. about 0.4-0.7 or 0.7-1.0 mm.

Active Substance

The active substance in the formulations according to the invention may be any active substance which is advantageously administered in 10 a controlled release multiple-units formulation. Examples of suitable active substances are found among almost all therapeutic groups, including diuretics, antiepileptics, sedatives, antiarrhythmics, anti-rheumatics, β -blockers, vasodilators, analgesics, bronchodilators, hormones, vitamins, oral antidiabetics, antibiotics, antihypertensives, 15 antiinflammatory drugs, antimicrobial agents and antidepressants, polypeptides (enkephalines and endorphines), enzymes and mucopolysaccharides.

As examples of active substances may be mentioned pindolol, quinidine salts, lithium carbonate, acetaminophen, vincamine, dipyridamol, theophylline, 20 dextropropoxyphene, amitriptyline, hydralazine, digoxin, furosemide, propranolol, ibuprofen, lidocaine, mepyrmine, nitroglycerin, clonidine, disopyramide, verapamil, captopril, prazosin, nifedipine, paracetamol and indomethacin.

Among these substances, some are characterized as having a pH-dependent solubility, others as having a pH-independent solubility. Active substances having a pH-dependent solubility (that is, a solubility which differs corresponding to a ratio of $10:10^3$ over the physiological pH range of 1-7.5) are preferably incorporated in cores in combination with buffer substances such as discussed above, in order 25 to obtain a dissolution of active substance which is substantially independent of the gastrointestinal pH variations through which the units pass. 30

Especially important formulations according to the invention are formulations in which the active substance, apart from being a substance about which it is known or indicated from a pharmacokinetic and/or clinical point of view that it is advantageously administered in a controlled release multiple-units formulation, is a substance which exerts an irritating effect on the gastrointestinal mucosa such as acetylsalicylic acid, potassium chloride, lithium salts, propionic acid derivatives, iron salts and magnesium salts.

In utilizing the principle of the invention, the units are freely distributed throughout the gastrointestinal tract, independent of gastric emptying, as the units are small enough to pass the pylorus even when the sphincter is closed. This makes it possible to obtain a low concentration at the mucosa and thus to minimize the risk of local irritation.

15 *Coating*

The diffusion coating (i.e. usually the inner film layer) applied on the units according to the invention is a diffusion coating which is applied from a dispersion in water. The application of the coating is typically performed in a fluidized bed or by pan coating.

Examples of diffusion coating materials which may be used for the purpose of the present invention are coatings selected from the group consisting of acrylic polymers and copolymers, e.g., a polymerisate of acrylic acid ethylesters and methacrylic acid methylester such as Eudragit® E 30 D or ethylcellulose such as Aquacoat® ECD-30. Enteric coating materials such as hydroxypropylmethylcellulosephthalate, e.g. HP 50 or HP 55, polyvinylacetatephthalate, e.g. Coateric®, celluloseacetatephthalate and the like may also be employed according to the same principles.

Coating compositions containing a hydrophobic substance are preferably applied in the form of a suspension of particles of the hydrophobic substance at a temperature below the melting or softening temperature of the hydrophobic substance. Normally, it is preferred

to disperse the hydrophobic substance in water, optionally together with the anti-adhesive (which preferably forms agglomerates with the hydrophobic substance), by heating to about the melting or softening point of the hydrophobic substance, dispersing, and subsequently cooling. The dispersion is then added to the aqueous dispersion of the film-forming substance.

Coating compositions containing a polymeric substance such as a water-soluble polymer as the reinforcing agent, e.g. hydroxypropylmethylcellulose which in fact is the preferred substance, are suitably prepared by heating water to a temperature at which the hydroxypropylmethylcellulose is not soluble in water (i.e. a temperature above about 60°C), the anti-adhesive such as talc is dispersed in the hot water, which is an advantage as, at the higher temperature, there is less surface tension, and the hydroxypropylmethylcellulose is dispersed in the mixture in the form of discrete particles. After dispersion, the mixture is slowly cooled to below about 60°C with stirring so that the hydroxypropylmethylcellulose is dissolved. The film-forming agent is then added to the resulting cooled mixture with stirring until a homogeneous mixture is obtained.

The coating material may be admixed with various excipients such as plasticizers, inert fillers, and pigments, in a manner known *per se*.

Examples of plasticizers include triacetin, Myvacet™ 9-40T (acetylated monoglyceride), rape oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylfumarate, diethylsuccinate, diethylmalonate, diethyltartrate, tri-n-butylcitrate, dibutylphthalate, diethylphthalate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol, and mixtures thereof. The plasticizer is normally incorporated in an amount of 1-30%, calculated on the dry matter content of the coating mixture.

However, according to the invention, it has been found that for certain polymers, in particular an acrylic polymer such as a copolymer of acrylic acid methyl ester and methacrylic acid methyl ester, a

plasticizer may not be necessary, and hence, a particular aspect of the invention provides units coated with a plasticizer-free coating, in particular a coating based on a copolymerisate of acrylic acid ethylester and methacrylic acid methylester as the film-forming polymer, of the type according to the invention.

The amount of inner film layer applied is adapted so as to obtain a predetermined dissolution characteristic of the coated units. Normally, the amount of the inner film layer will be about 1-30% by weight, especially about 5-25%, particularly about 15%, by weight of the uncoated units depending on the predetermined dissolution characteristics of the active substance and the desired release profile.

The amount of dry matter in the film-coating mixture will normally be about 1-50%, especially 5-30%, and typically about 20%. It is advantageous to have a high dry matter content in the film-coating mixture as this reduces the coating time necessary to obtain an adequate coating of the units.

As mentioned above, hydroxypropylmethylcellulose is a preferred film-forming agent for the outer film layer. Apart from being anti-adhesive at elevated temperatures, the currently preferred hydroxypropylmethylcellulose, e.g. Methocel® E5 premium or Pharmacoat® 606, has a low viscosity in an aqueous solution so that it is possible to obtain as high a dry matter content as 6-8%. This means that a reduction of the coating time is obtained for the outer film layer as well. When using hydroxypropylmethylcellulose, it may be advantageous to incorporate a plasticizer such as one of the plasticizers mentioned above. Similarly, surfactants, pigments and other conventional additives may be incorporated in a manner known *per se*.

Dosage forms

The units prepared according to the invention may be incorporated in normal pharmaceutical dosage forms or formulations such as capsules containing a multiplicity of the units, sachets containing a multiplicity of the units, or tablets which will disintegrate substantially immediately.

tely upon ingestion in the stomach to form a multiplicity of individual units.

A favoured tablet according to the invention is one in which the multiplicity of units are coated crystals or coated cores of the type defined above which are compressed together with about 25-40% of conventional tableting excipients to a tablet hardness of at least about 4 kp (as measured by means of a Schleuniger apparatus as described below) without any significant change in release characteristics relative to non-compressed units of the same composition.

10 The adjuvants and excipients used in the preparation of disintegratable tablets are of the same kind as conventionally used in the pharmaceutical industry for this purpose. Examples of filler or diluents useful for preparing tablets according to the invention are lactose, sucrose, dextrose, mannitol, calcium sulphate, dicalcium phosphate, 15 tricalcium phosphate, starches such as rice starch and microcrystalline cellulose. Useful binders are acacia, tragacanth, gelatine, sucrose, pregelatinized starch, starch, sodium alginate, ammonium calcium alginate, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, 20 magnesium aluminium silicate, and polyacrylamides. As examples of disintegrants may be mentioned cross-linked polyvinylpyrrolidone, starch derivatives such as sodium carboxymethylcellulose, and cellulose derivatives. As lubricants, "gliders" and "anti-adhesives" may be mentioned metallic stearates, talc, high melting point waxes, and 25 colloidal silica.

When it is desired to use excipients or adjuvants for the preparation of sachets or capsules, such as fillers and lubricants, these may be of the same type as described above.

The filling of capsules and sachets and the compression of tablets are 30 performed in a manner known *per se*.

MATERIALS AND METHODS

In the examples, the following materials were used:

	Sodium dihydrogen phosphate:	Anhydrous. Analyzed according to BP 80.
5	Sucrose powder:	Ph. Eur.
	Microcrystalline cellulose:	BPC 79. Avicel® supplied by FMC, Philadelphia.
10	Talc:	Ph. Eur. and additionally complying with the following requirements:
15		About 0.002 g of talc is distributed in 1 drop of cyclohexanol and investigated under microscope. 45 particles out of 50 may not be above 40 µm.
	Potassium chloride:	Ph.Eur.
20	Hydroxypropylmethylcellulose:	USP 20. Methocel® E5 premium. Supplied by Dow Chemicals, Michigan, USA. Abbreviated to HPMC.
	Propranolol hydrochloride:	BP 80.
25	Sodium carboxymethylcellulose:	USP 20. Blanose® 7 LFD. Supplied by Hrcules through Scandibutor, Copenhagen, Denmark.

Purified water:

Ph. Eur.

Eudragit® E 30 D:

A neutral acrylic acid ethylester/
methacrylic acid methylester
copolymerisate in the ratio 70:30,
molecular weight above 800,000,
as a 30% aqueous dispersion,
supplied by Röhm Pharma GmbH,
Darmstadt, Germany.

5

Rice starch:

Ph.Eur./USP 20.

10 Magnesium stearate:

Ph.Eur./USP 20.

Determination of *in vitro* dissolution characteristics:

In vitro dissolution rates were determined according to Baggesen et al. (1981). The rotation speed was 30 ± 1 r.p.m., and the dissolution medium was 25 ml of 0.1 M hydrochloric acid (pH 1.2), maintained at $37 \pm 0.1^\circ\text{C}$.

15

Release of propranolol into the dissolution medium was determined by means of UV spectrometry at 290 nm.

Release of potassium chloride into the dissolution medium was determined by means of a potassium-selective electrode.

20 Disintegration time of tablets was measured according to Ph.Eur. 2nd Ed. I, V.5.1.1.

Tablet hardness was determined in a Schleuniger-2E apparatus available from Dr. K. Schluniger & Co., Switzerland, in kp.

25 The tabletting machine employed was an Xcenter press single-punch machine TM 20.

Calculation of the Dissolution Index

In the range of 20-80% drug released, an estimation was performed for at least four pairs of figures, e.g., t_{20} , t_{35} , t_{50} , t_{65} , of corresponding times for the two profiles so as to release the same amount of drug.

The correlated values were plotted in a time-time coordinate system, with the abscissa as time for the dissolution profile in simulated gastric fluid and the ordinate as the time in the simulated intestinal fluid.

- 10 A linear regression analysis was performed (at least four points, excluding 0.0). Provided that the shape of the two profiles are similar a straight line through the origin is achieved.

The dissolution index is calculated as:

$$DI = (b-1) \cdot 100$$

- 15 where b is the slope.

When the formulation dissolves faster in simulated intestinal fluid than in simulated gastric juice the calculated DI value will be negative.

The limit of pH-independency is a DI of ≤ 25 .

EXAMPLE 1

- 20 Preparation of Film-Coated Potassium Chloride Crystals

Preparation of Inner Film-Coating Composition Containing a Polymeric Substance

An inner film-coating composition was prepared from the following ingredients:

	Eudragit® E 30 D	43.3%
	Methocel® E5	0.65%
	Talc	1.35%
5	Purified Water	to 100% (= 15% dry matter)

Water was heated to 80°C and talc was dispersed therein by means of a disperser. To the heated mixture was added Methocel® E5 premium which was dispersed in the form of discrete particles. This dispersion
10 was slowly cooled to room temperature with stirring causing the HPMC to dissolve. The Eudragit® E 30 D was added with stirring.

Application of Inner Film-Coating Composition on Potassium Chloride Crystals

The film-coating composition prepared as described above at ambient
15 temperature was sprayed onto the potassium chloride crystals in a fluidized bed using an outlet air temperature of max. 40°C.

Preparation of Outer Film-Coating Composition

A film-coating composition was prepared from the following ingredients:

20

Methocel® E5 premium	6%
Talc	6%
Purified water	92%
	100% (= 12% dry matter)

25

Water was heated to 80 C and talc was dispersed therein by means of a disperser. To the heated mixture was added Methocel® E5 premium which was dispersed in the form of discrete particles. This dispersion was slowly cooled to room temperature with stirring causing the HPMC
5 to dissolve.

Application of Outer Film-Coating Composition on Potassium Chloride Crystals

The outer film-coating composition prepared as described above was sprayed onto the potassium chloride crystals already coated with the
10 inner film layer in a fluidized bed using an outlet air temperature of max. 40°C. The outlet air temperature was then raised to 70°C for 1 hour followed by cooling. The presence of the outer film layer makes this heat treatment possible without causing agglomeration of the coated crystals, which would have occurred if the crystals had been
15 coated with the inner film layer only.

The amount of inner film layer applied was 13% and the amount of outer film layer was 1%, by weight of the uncoated crystals.

The release of potassium was measured as described in MATERIALS AND METHODS.

20 It appears from Table 1 that a prolonged dissolution profile has been obtained.

TABLE 1

Percentage of Potassium Released at pH = 1.2 (n=3) after			
5	1 h	2 h	6 h
	23.40 (s=0.96)	52.97 (s=2.09)	90.86 (s=2.39)

EXAMPLE 2**10 The Effect of Heating with Respect to the Dissolution Characteristics of the Film-Coated Crystals**

Inner and outer film-coating compositions were prepared and applied as described in Example 1 with the exception that, in one experiment, no heating of the coated units took place.

15 The release of potassium was determined as described in MATERIALS AND METHODS.

TABLE 2

Percentage of Potassium Released at pH = 1.2 after 1 hour (n=3)			
5	Time	0	2 weeks
10	No heating	41.85	37.14
		(s=1.52)	(s=2.73)
	Heating at 70°C for 1 h	22.89	23.40
		(s=0.87)	(s=0.96)

It appears from Table 2 that the release of potassium from the unheated units has decreased after a week, while remaining constant from the heat-treated units.

15 EXAMPLE 3

Preparation of Film-Coated Potassium Chloride Crystals

Preparation of Inner Film-Coating Composition Containing a Hydrophobic Substance

20 A film-coating composition was prepared from the following ingredients:

25	Eudragit® E 30 D	47.6%
	Paraffin	2.9%
	Talc	2.9%
	Purified Water	46.6%
	100% (equals 20% dry matter)	

The paraffin was heated in purified water (14% of the 47.3% of purified water as stated above) to a temperature well above the melting point of paraffin, i.e. between 70 and 80°C. The heated mixture was treated with a disperser under addition of talc. The mixture was cooled to about 30°C under continued dispersion, and Eudragit® E 30 D was added with stirring. This film-coating composition was sieved and finally diluted to a dry matter content of 20% using 33.3% of water.

The film-coating composition prepared as described above was applied on potassium chloride crystals as described in Example 1.

The outer film-forming composition was prepared and applied as described in Example 1.

The amount of inner film layer applied was 14% and the amount of outer film layer was 1%, by weight of the uncoated crystals.

The release of potassium was measured as described in MATERIALS AND METHODS.

It appears from Table 3 that a prolonged dissolution profile has been obtained.

TABLE 3

Percentage of Potassium Released at pH = 1.2 (n=3) after			
	1 h	2 h	6 h
	24.21 (s=0.62)	51.04 (s=2.69)	92.13 (s=0.16)

Preparation of a Pharmaceutical Dosage Form

The film-coated crystals prepared as described above may be filled into a capsule size No. 1 and No. 00. Each capsule comprises 300 mg and 600 mg of potassium chloride, respectively. The same film-coated crystals may be filled into sachets to comprise a pharmaceutical dosage form of 1000 mg or more of potassium chloride. The film-coated crystals may also be granulated and compressed into tablets of different shapes, each comprising 600 mg or 750 mg of potassium chloride, respectively, e.g. a tablet substantially as shown in the appended drawing.

EXAMPLE 4**The Effect of Different Amounts of Dry Matter on the Release of Potassium from Film-Coated Crystals**

Inner and outer film-coating compositions were prepared as described in Example 1 and 3. The inner film coating composition was applied in varying amounts as shown in Table 4a and 4b below. The outer film-coating composition was applied as described in Example 1.

The release of potassium was measured as described in MATERIALS AND METHODS.

TABLE 4a

Percentage of Potassium Released at pH = 1.2 after 1 hour (n=3)				
Dry matter ¹	8%	10%	13%	15%
	95.19	72.76	22.89	12.57
	(s=1.13)	(s=1.64)	(s=0.87)	(s=0.62)

10 ¹ by weight of coating solids, calculated on the weight of the uncoated crystals. Inner film layer according to Example 1.

TABLE 4b

Percentage of Potassium Released at pH = 1.2 after 1 hour (n=3)			
Dry matter ¹	10.0%	12.0%	14.0%
	30.44	25.79	23.64
	(s=1.12)	(s=1.06)	(s=0.78)

20 ¹ by weight of coating solids, calculated on the weight of the uncoated crystals. Inner film layer according to Example 3.

It appears from Table 4a and 4b that the release of potassium is correlated to the amount of inner film applied so that a reduction in release may be obtained by increasing the amount of dry matter in the inner film layer.

EXAMPLE 5

The Effect of Paraffin Added to the Film-Coating Composition with Respect to the Dissolution Characteristics of the Film-Coated Crystals. Hydrophobic Effect before and after Heat Treatment

5 Preparation of Inner Film-Coating Composition

Inner film-coating compositions were prepared from the following ingredients:

	A	B	C
10 Eudragit® E 30 D	47.6%	41.7%	37.6%
Paraffin	2.9%	3.8%	4.4%
Talc	2.9%	3.8%	4.4%
Purified water	46.6%	50.7%	54.2%
15	100.0%	100.0%	100.0%
	(=20% dry matter)	(=20% dry matter)	(=20% dry matter)

as described in Example 3.

20 Application of the Inner Film-Coating Composition on Crystals

Film-coating mixtures A, B and C were all applied on potassium chloride crystals in an amount corresponding to 10% of the Eudragit® E 30 D (dry matter).

25 The outer film-coating composition was applied as described in Example 1 in an amount of 1% (dry matter).

The release of potassium was measured as described in MATERIALS AND METHODS.

TABLE 5

Percentage of Potassium Released at pH = 1.2 after 1 hour (n=3)				
5	Film-coating mixture	A	B	C
	Percent of paraffin	2	3	4
	No heat treatment	18.21 (s=2.67)	19.88 (s=1.33)	20.83 (s=0.55)
	Heat treatment for	14.91	14.80	12.30
10	1 hour at 70°C	(s=0.07)	(s=0.24)	(s=0.40)
	Reduction in release (%)	3.30	5.08	8.53

15 It appears from Table 5 that, prior to heating, paraffin has no sustained-release effect. After heating, a notable reduction in release is observed which increases with increasing amounts of paraffin.

EXAMPLE 6

The Effect of Hydroxypropylmethylcellulose on the Release of Potassium from the Coated Crystals

20 *Preparation of Inner Film-Coating Composition*

Inner film-coating compositions were prepared from the following ingredients:

	A	B	C
5			
Eudragit® E 30 D	44.3%	43.2%	41.5%
Methocel® E5 prem.	0.3%	0.7%	1.2%
Talc	1.4%	1.4%	1.3%
Purified Water	to 100%	to 100%	to 100%
	(= 15% dry matter)	(= 15% dry matter)	(= 15% dry matter)
10			

The inner film-coating compositions were prepared and applied as described in Example 1 in an amount corresponding to 10% of the Eudragit® E 30 D (dry matter).

15 The outer film-coating composition was prepared and applied as described in Example 1.

The release of potassium chloride was measured as described in MATERIALS AND METHODS.

TABLE 6

20	Percentage of Potassium Released at pH = 1.2 after 1 hour (n=3)			
	Film-coating mixture	A	B	C
	Percent of HPMC ¹	2.5	5	10
25		20.05	25.49	37.34
		(s=0.31)	(s=1.74)	(s=1.04)

¹ Calculated as dry matter on the amount of Eudragit® and Methocel.

It appears from Table 6 that the release of potassium increases with the amount of HPMC added to the film-coating composition. This means that HPMC should be incorporated in amounts which are sufficient to impart compressibility to the coating, but not sufficient to impair the release characteristics of the inner film layer.

EXAMPLE 7

Tabletting of Coated Potassium Chloride Crystals

Coated potassium chloride crystals prepared as described in Example 1 and 3 were compressed to tablets with 27.3% of excipients in an eccentric press single-punch tabletting machine TM 20 to a hardness of 7.6 kp and 11.0 kp (n=6), respectively. The resulting tablets had a gross weight of about 1200 mg, corresponding to 750 mg of KCl. The disintegration time of the tablets was 3 and 2 minutes, respectively.

The release of potassium was measured as described in MATERIALS AND METHODS.

TABLE 7a

Coated Crystals According to Example 1

Percentage of Potassium Released at pH = 1.2 (n=3) after				
Crystals	1 h	2 h	6 h	
	23.40 (s=0.96)	52.97 (s=2.09)	90.86 (s=2.39)	
Tablets	1 h	2 h	6 h	
	22.89 (s=0.98)	54.42 (s=1.45)	94.30 (s=1.18)	

TABLE 7b

Coated Crystals According to Example 3

Percentage of Potassium Released at pH = 1.2 (n=3) after			
	1 h	2 h	6 h
Crystals	24.21 (s=0.62)	51.04 (s=2.69)	92.13 (s=0.16)
Tablets	23.62 (s=0.67)	50.07 (s=0.94)	88.92 (s=2.03)

It appears from Table 7a and 7b that there is correlation between the results obtained for compressed coated crystals and non-compressed coated crystals.

EXAMPLE 8

Preparation and Tableting of Coated Cores

Preparation of Cores

Cores were prepared from the following ingredients:

Propranolol hydrochloride	60%
Microcrystalline cellulose	22%
Sodium dihydrogenphosphate	15%
Sodium carboxymethylcellulose	1%
Eudragit® E 30 D	2% (dry matter)
	100%

A mixture of the above ingredients was moistened with purified water and mixed until the mixture was a little grainy.

5 The moist mixture was extruded through a 0.75 mm sieve. The resulting extrudate consisted of strings breaking off in lengths of a few cm.

The extruded strings were formed into compact-shaped cores in a marumerizer. The resulting compact-shaped cores had a size of about 0.7-1.0 mm.

10 Inner and outer film-coating compositions were prepared and applied as described in Example 1.

The coated cores were compressed into tablets with 40% of conventional excipients on the tableting machine specified in MATERIALS AND METHODS.

15 The tablets had a weight of 500 mg, corresponding to 162.2 mg of propranolol hydrochloride per tablet.

Tablet hardness was 6.3 kp when measured as described in MATERIALS AND METHODS.

The disintegration time was <1 minute.

20 The propranolol released was measured as described in MATERIALS AND METHODS.

TABLE 8

Percentage of propranolol released at pH = 1.2 (n=3) after				
5		1 h	2 h	6 h
	Cores	23.26 (s=0.25)	40.86 (s=0.64)	77.54 (s=0.14)
	Tablets	27.28 (s=0.92)	45.79 (s=0.47)	79.74 (s=1.46)
Percentage of propranolol released at pH = 7.5 (n=3) after				
10		1 h	2 h	6 h
	Cores	28.75 (s=0.11)	51.30 (s=0.80)	82.00 (s=0.56)
15	Tablets	31.96 (s=0.32)	55.16 (s=0.35)	82.46 (s=1.10)

It appears from Table 8 that there is no significant difference in the release of propranolol from cores and tablets, respectively. The dissolution index is 4 determined as described in MATERIALS AND METHODS which means that the release is pH-independent.

EXAMPLE 9

Preparation of Film-Coated Cores

25 *Preparation of Cores*

Cores were prepared from the following ingredients:

5	Caffein	20%
	Sodium dihydrogen phosphate	20%
	Microcrystalline cellulose	29%
	Talc	19%
	Sucrose powder	7%
	Methocel® E5 premium	3%
	Methocel® E15 premium	2%
		100%
10		

as described in Example 8.

Inner and outer film-coating compositions were prepared and applied as described in Example 3.

The caffeine released into the dissolution medium was measured as described in MATERIALS AND METHODS.

TABLE 9

Percentage of Caffeine Released at pH = 1.2 (n=3) ¹ after			
20	1 h	2 h	6 h
	19.13	30.25	65.67
	(s=0.98)	(s=1.31)	(s=1.38)

¹ The amount of inner film layer is 5% by weight of the uncoated cores.

It appears from Table 9 that a prolonged dissolution profile has been obtained.

Preparation of Pharmaceutical Dosage Form

The film-coated cores prepared as above may be filled into capsules or sachets.

EXAMPLE 10

- 5 The Effect of the Amount of Dry Matter Applied to Cores with Respect to the Dissolution Characteristics of the Coated Cores

Inner and outer film-coating compositions were prepared and applied as described in Example 3.

- 10 The caffeine released into the dissolution medium was measured as described in MATERIALS AND METHODS.

TABLE 10

Percentage of Caffeine Released at pH = 1.2 (n=3) after 1 hour				
15	Dry matter ¹	3%	5%	8%
		50.79	19.13	10.75
		(s=1.38)	(s=0.98)	(s=1.36)

- 20 ¹ Dry matter by weight of coating solids, calculated on the weight of the uncoated cores.

It appears from Table 10 that the release of caffeine is correlated to the amount of dry matter applied to the cores, i.e. by increasing the amount of dry matter the dissolution of caffeine is diminished.

EXAMPLE 11

The Effect of the Dry Matter Content in the Inner Film-Coating Composition

- 5 Inner and outer film-coating compositions were prepared and applied as described in Example 1 with the exception that the dry matter content of the inner film-coating composition was 15%, 20%, 25% and 30%, respectively, in different experiments.

All crystals were coated with 15% of dry matter relative to the weight of the uncoated crystals.

- 10 The release of potassium was measured as described in MATERIALS AND METHODS.

TABLE 11

15

Percentage of Potassium Released at pH = 1.2 (n=3) after				
% of dry matter	15	20	25	30
	23.13	21.58	29.06	27.57
	(s=0.82)	(s=0.14)	(s=0.53)	(s=1.11)

- 20 It appears from Table 11 that it is possible to use film-coating compositions with as high a dry matter content as 30% without any significant change in release. This is important as a high dry matter content will lead to a shorter coating period.

LITERATURE

GB Patent 1 468 172

European Patent Application 79 850 110, Publication No. 0 013 262

US Patent 4 193 985

- 5 Baggensen S, Bechgaard H, & Schmidt K, "Content and dissolution uniformity testing of controlled-release products: The Repro-Dose® quality control procedure", *Pharm. Acta Helv* 56, 1981, pp. 85-92.

- Bechgaard, H & Heggermann Nielsen, G, "Controlled release multiple-units and single-units doses. A literature review", *Drug Develop Ind Pharm* 4, 1978, pp. 53-67.

Bechgaard, H & Ladefoged, K, "Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets", *J Pharm Pharmacol* 30, 1978, pp. 690-692.

- Bechgaard, H & Baggensen, S, "Propoxyphene and norpropoxyphene: 15 Influence of type of controlled release formulation on intra- and intersubject variations", *J Pharm Sci* 69, 1980, pp. 1327-1330.

Bogentoft, C, Carlsson, I, Ekenved, G & Magnusson, A, "Influence of food on the absorption of acetylsalicylic acid from enteric-coated dosage forms", *Eur J Clin Pharmacol* 14, 1978, pp. 351-355.

- 20 Green, DM, "Tablets of coated aspirin microspherules - A new dosage form", *J New Drugs* 6, 1966, pp. 294-303.

McDonald, PJ, Mather, LE & Story, MJ, "Studies on absorption of a newly developed enteric-coated erythromycin base", *J Clin Pharmacol* 17, 1977, pp. 601-606.

- 25 Snedecor, GW & Cochran, WG, *Statistical Methods*. Iowa State University Press, Iowa, 1967, pp. 271-275.

CLAIMS

1. An oral pharmaceutical controlled release multiple-units formulation in which individual units containing an active substance are coated with a substantially water-insoluble, but water-diffusible controlled release coating which includes
- 5
- 1) an inner film layer which causes adhesion between the units at elevated temperatures, comprising a water-dispersible film-forming agent, and
 - 2) an outer film layer comprising a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units.
- 10
2. A formulation according to claim 1, in which the inner film layer additionally comprises a substance which, in itself, is capable of forming a continuous phase.
- 15
3. A formulation according to claim 2, in which the substance is a hydrophobic substance, and the outer film layer is impermeable, at temperatures above the melting point of the hydrophobic substance, to the molten hydrophobic substance.
4. A formulation according to claim 2, in which the substance is a polymeric substance which imparts compressibility to the coating.
- 20
5. A formulation according to any of claims 1-4, in which the film-forming agent of the inner film layer is selected from cellulose derivatives, silicone polymers and copolymers, vinyl polymers and copolymers, biodegradable polymers such as polyamino acids, polylactic acid and copolymers and derivatives thereof, and acrylic polymers and copolymers, or mixtures thereof.
- 25
6. A formulation according to claim 5, in which the film-forming agent is selected from hydroxyethyl cellulose and a copolymer of poly(meth)-

acrylic acid esters, hydroxypropylmethylcellulose phthalate, cellulose-acetate phthalate, polyvinylacetatephthalate and vinylacetate-crotonic acid copolymerisates.

7. A formulation according to claim 3, in which the hydrophobic substance of the inner film layer is selected from hydrocarbons and hydrocarbon derivatives, waxes, oils and fats, and mixtures thereof, especially a waxy substance such as paraffin wax.

8. A formulation according to claims 3 or 7, in which the hydrophobic substance is present in an amount of between about 0.1 and 50%, in particular between 1 and 40%, especially between about 10 and 30%, by weight of the inner film layer.

9. A formulation according to claim 4, in which the polymeric substance in the inner film coating is selected from polyvinylpyrrolidone, polyalkylene glycols such as polyethylene glycol, and cellulose derivatives such as hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

10. A formulation according to claim 9, in which the polymeric substance is present in an amount between 1 and 10%, such as an amount between 2% and 8%, especially an amount of about 4% by weight relative to the amount of film-forming agent in the inner film layer.

11. A formulation according to any of the preceding claims, in which the inner film layer comprises an anti-adhesive which is a finely divided, substantially water-insoluble, pharmaceutically acceptable, non-wetting powder.

12. A formulation according to claim 11, in which the anti-adhesive is present in an amount of between about 0.1 and 50%, preferably between about 1 and 40%, especially about 10-30% such as about 15% by weight of the inner film layer.

13. A formulation according to any of claims 1-12, in which the inner film layer is present in an amount of about 1-30%, especially about 5-25%, in particular about 15%, by weight of the uncoated units.

14. A formulation according to any of claims 1-13, in which the film-forming agent of the outer film layer is one which is anti-adhesive at temperatures above about 40°C, especially temperatures above about 50°C, such as a temperature between about 60°C and about 120°C.

15. A formulation according to claim 14, in which the film-forming agent of the outer film layer is selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulose-phthalate, celluloseacetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose, or hydroxypropylmethylcellulose.

16. A formulation according to claim 14 or 15, in which the film-forming agent of the outer film layer is present in an amount of about 0.1-10%, especially 0.5-5%, in particular about 1% by weight of the uncoated unit.

17. A formulation according to any of claims 14-16, in which the outer film coating additionally comprises a lubricant which is a finely divided pharmaceutically acceptable powder.

18. A formulation according to any of the preceding claims, in which the units are crystals of a size between 0.1 and 1.5 mm.

19. A formulation according to any of claims 1-17, in which the units are cross-sectionally substantially homogeneous cores of a size of about 0.1-1.5 mm, in particular about 0.4-1.0 mm, such as about 0.4-0.7 mm or 0.7-1.0 mm.

20. A method of preparing an oral pharmaceutical controlled release multiple-units formulation as claimed in any of claims 1-19, in which

5 a) individual units containing an active substance are coated with a coating composition comprising an aqueous dispersion of a film-forming agent to form an inner film layer which causes adhesion between the units at elevated temperatures,

10 b) the thus coated units are provided with an outer film layer of a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the coated units, and

15 c) the coated units are subsequently heated to a temperature at which the inner film layer is tacky, and at which the formation of a continuous phase of the film-forming agent is accelerated, and subsequently cooled, whereby a coating which substantially does not change its diffusion characteristics in the course of time is formed.

21. A method according to claim 20, in which the coating composition additionally comprises a substance which, in itself, is capable of forming a continuous phase.

20 22. A method according to claim 21, in which the substance is a hydrophobic substance, and the units coated according to steps a) and b) in the method of claim 20, after which steps the hydrophobic substance is present in the inner film layer as a dispersed phase, are heated to a temperature above the melting point of the hydrophobic substance which, on melting and subsequent cooling, forms a continuous phase in the inner film layer in homogeneous admixture with the film-forming agent, the outer film layer being one which is impermeable, at temperatures above the melting point of the hydrophobic substance, to the molten hydrophobic substance.

30 23. A method according to claim 21, in which the substance is a polymeric substance which, in step a) of the method of claim 20,

prev ents adhesion between the units and which imparts compr ssibility to th inner film lay r, and th units coat d according to st ps a) and b) in the method of claim 20 are heated to a temperature at which the film-forming agent forms a continuous phase in homogeneous admixture with the polymeric substance.

24. A method according to any of claims 20-23, in which the coated units are heated to a temperature above about 40°C, especially a temperature above about 50°C, such as a temperature between about 60°C and about 120°C.
- 10 25. An oral pharmaceutical controlled release composition which comprises a multiplicity of units as specified in any of claims 1-19 admixed with one or more pharmaceutically acceptable fillers, diluents, binders, lubricants or disintegrants.
- 15 26. A pharmaceutical composition according to claim 25 which is a tablet which disintegrates substantially immediately upon ingestion in the stomach into a multiplicity of individual units.

1/1

Fig. 1.

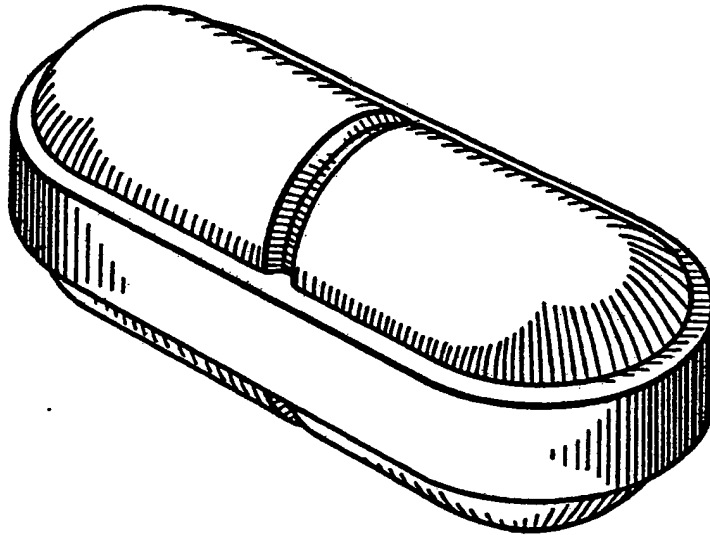
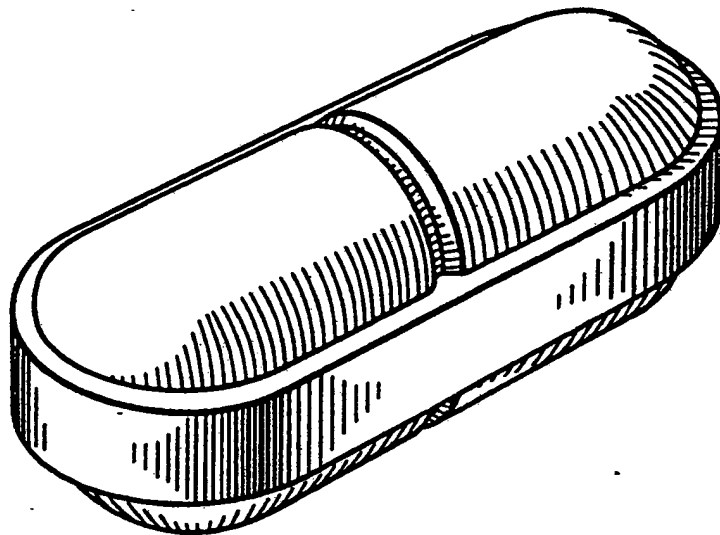



Fig. 2.



INTERNATIONAL SEARCH REPORT

International Application No PCT/DK85/00005

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC:		
A 61 K 9/14, A 61 K 9/22		
II. FIELDS SEARCHED		
Minimum Documentation Searched †		
Classification System	Classification Symbols	
IPC 4	A 61 K 9/14, 9/16, 9/22, 9/26, 9/32, 9/36, 9/42, 9/28, 9/58, 9/60, 9/62, 9/34, 9/54, 9/00; A 61 K 47/00 .../...	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ‡		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT*		
Category *	Citation of Document, †† with indication, where appropriate, of the relevant passages ‡‡	Relevant to Claim No. ‡‡
X	DE, A, 3 046 559 (ROUSSEL-UECLAF) 17 September 1981 & BE, 886558 GB, 2066070 FR, 2471186 NL, 8006659 JP, 56092817 SE, 8007639 AT, 373146 CA, 1157378 US, 4432966 CH, 645021	1-26
A	EP, A, 0 063 014 (SANKYO COMPANY LTD) 20 October 1982	
A	US, A, 2 928 770 (FRANK M. BARDANI) 15 March 1960	
A	US, A, 2 991 226 (CHARLES E. FROSST & CO) 4 July 1961 .../...	
* Special categories of cited documents: † "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1985-04-15	1985-04-26	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Terttu Gierer	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II

Fields Searched (cont).

National C1 30h:9/02

US C1 424:19, 20, 35, 21, 38V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
E	DE, A, 3 233 764 (R.P. SCHERER GMBH) 15 March 1984	1-26
E	US, A, 4 432 966 (ROUSSEL-UCLAF) 21 February 1984	1-26